UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/525,998	03/15/2000	Rudolph Hauptmann	98.385-E	1361

20306 7590 07/29/2005

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/525,998	HAUPTMANN ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 27,49,64,67,68,71-74,76,77,79,81-86,89-91,94,96,97,102,104,105,110,111,114-116,119,121-123,126,128-135,138,139,144-168,170,172 and 174-178.

Continuation of Disposition of Claims: Claims rejected are 27,49,64,67,68,71-74,76,77,79,81-86,89-91,94,96,97,102,104,105,110,111,114-116,119,121-123,126,128-135,138,139,144-168,170,172 and 174-178.

DETAILED ACTION

Claims Status

1. Claims 27, 49, 64, 67, 68, 71-74, 76, 77, 79, 81-86, 89-91, 94, 96, 97, 102, 104, 105, 110, 111, 114-116, 119, 121-123, 126, 128-135, 138, 139, 144-168, 170, 172 and 174-178 are pending in the instant application.

Withdrawn Rejections

2. The rejection of claims under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-63 of U.S. Patent No. 6,440,693 is withdrawn in view of Applicants' terminal disclaimer filed May 18, 2005.

New Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 97, 102, 104, 168, 170 and 172 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to a broad genus of host cells comprising a vector which, in turn, comprises the claimed DNA.

On page 28, lines 12-17, the specification states:

"The present invention encompasses the expression of the desired TNF binding protein in either prokaryotic or eukaryotic cells. Preferred eukaryotic hosts include yeast (especially Saccharomyces), fungi (especially Aspergillus), mammalian cells (such as, for example, human or primate cells) either *in vivo*, or in tissue culture."

Because the specification contemplates human host cells *in vivo*, it is implied that the specification contemplates transgenic humans. If the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. 101 must be made indicating that the claimed invention is directed to nonstatutory subject matter. Furthermore, the claimed invention must be examined with regard to all issues pertinent to patentability, and any applicable rejections under 35 U.S.C. 102, 103, or 112 must also be made.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 116, 119 and 130 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4.1 Claims 116 and 119 are indefinite because they recite the limitation "wherein the prokaryotic cell". There is insufficient antecedent basis for this limitation in the claims because they depend from claims 105 and 111 respectively, which do not recite a prokaryotic cell.

4.2 Claim 130 is indefinite because it encompasses a recombinant host cell containing a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO: 2. However, it depends from claim 104 which depends from claim 67, which is drawn to an isolated nucleic acid molecule encoding a polypeptide consisting of the amino acid sequence of SEQ ID NO: 4, which is a smaller fragment of the larger polypeptide of SEQ ID NO: 2.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 97, 102, 104, 168, 170 and 172 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated or cultured host cell comprising a vector, does not reasonably provide enablement for a host cell comprising a vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a broad genus of host cells comprising a vector which, in turn, comprises the claimed DNA.

On page 28, lines 12-17, the specification states:

"The present invention encompasses the expression of the desired TNF binding protein in either prokaryotic or eukaryotic cells. Preferred eukaryotic hosts include yeast (especially Saccharomyces), fungi (especially Aspergillus), mammalian cells (such as, for example, human or primate cells) either *in vivo*, or in tissue culture."

Because the specification contemplates mammalian host cells *in vivo*, it is implied that the specification contemplates three subgenera in which such host cells can be made and used. Specifically, the specification contemplates making and using the host cells in culture, in gene therapy, and in multicellular, transgenic organisms.

Case law directs that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more than is normally required in the art. *Atlas*

Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Ibid.*; *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). Since the instant specification contemplates that the claimed host cells can be made and used in three contexts, two of which are not enabled for the reasons set forth below, the instant fact pattern corresponds to the second situation wherein the claims encompass a significant number of inoperative embodiments and thus should be rejected under 35 U.S.C. § 112, first paragraph, as not being enabled for the full scope of the claims.

The specification contemplates that host cells can be made and used in three contexts. 1) The specification contemplates making and using isolated host cells in culture to produce the encoded protein recombinantly. Such is enabled, since the specification and prior art provide specific guidance on how to make and use host cells for this purpose. Undue experimentation would not have been required of the skilled artisan to make and use the claimed host cells in this context.

2) The specification also contemplates that the claimed gene products can be expressed in transgenic animals. However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated claimed gene is demonstrated to express the encoded peptide. There are also no methods or working examples in the specification indicating that a multicellular animal has the claimed gene "knocked out". The

unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Additionally, for example, the specification discloses that two possible techniques used to introduce the claimed transgene into animals include pronuclear microinjection and gene targeting in embryonic stem cells. However, the literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod Fert Dev 6: 585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even more rare than random events. Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected embryos, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals according to the instant invention. Furthermore, regarding gene targeting in embryonic stem cells, the specification does not provide guidance for identifying and isolating embryonic stem cells or for identifying other embryonal cells which are capable of contributing to the

germline of any animal. Campbell et al. teaches that, "in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species...However, as yet there are not reports of any cell lines which contribute to the germ line in any species other than mouse" (Campbell et al. Theriology 47(1): 63-72, 1997; see pg 65, 2nd paragraph). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells which can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

3) The specification also discloses that nucleotide constructs comprising the claimed gene can be used to genetically engineer host cells to express such products in vivo, which encompasses gene therapy approaches. However, the specification does not teach any methods or working examples that indicate the claimed nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the claimed nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene

therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into the cell of an organism to treat disease. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the disclosed protein and to introduce and express the claimed nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Please note that this rejection could be overcome by amending the claims to recite, for example, "An isolated host cell..." because such an amendment would clarify that the claims are

directed only to host cells which are to be made and used in culture as described in context 1) above.

Priority

6. This application is a continuation of 09/525,998, which is a division of 08/383,676, now patent 6,294,352, which is a continuation of 08/153,287, which is a continuation of 07/821,750, which is a division of 07/511,430. The Examiner notes that certified copies of the German priority documents P39 13 101.7, P3290 282.8 and European priority document 90106624.1 are present in the parent file 07/511,430. However, Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38F.3d551,32 USPQ 2d 1077 (Fed. Cir. 1994). The first priority document, 39 13 101.7, filed April 21, 1989, contains only fragments of the claimed polypeptides. The second priority document, 3920 282.8, filed June 21, 1989, discloses a polypeptide comprising amino acids 1-371 of the amino acid sequence of the full-length polypeptide of SEQ ID NO: 2. The third foreign priority document, 90106624.2, filed April 6, 1990, discloses the entire amino acid sequence of SEQ ID NO: 2 (455 amino acids). SEQ ID NOS: 4, 6, 8, 10, 12, 14, 16, 18 and 20 are contained within the first 172 amino acids of SEQ ID NO: 2, therefore the priority date accorded to those sequences is June 21, 1989. However, the priority date for the full length protein of SEQ ID NO: 2 is April 6, 1990.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 27, 49, 64, 67, 68, 71-74, 76, 77, 79, 81-86, 89-91, 94, 96, 97, 102, 104, 105, 110, 111, 114-116, 119, 121-123, 126, 128-135, 138, 139, 144-168, 170, 172 and 174-178 are rejected under 35 U.S.C. 102(e) as being anticipated by Wallach et al., U.S. Patent No. 5,695,953, effectively filing date Sept. 12, 1988.

Claims 27, 49, 64, 67, 68, 71-74, 76, 77, 79, 81-86, 89-91, 94, 96, 97, 102, 104, 105, 110, 111, 114-116, 119, 121-123, 126, 128-135, 138, 139, 144-168, 170, 172 and 174-178 are directed to nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO: 3 or encoding the protein of SEQ ID NO: 4, vectors and host cells which may be E. coli, yeast cell, Chinese Hamster Ovary cell, method of making the protein and recovering it, wherein the protein is formulated to comprise the polypeptide with a pharmaceutically acceptable carrier.

Wallach et al. claim a nucleic acid molecule comprising the nucleotide sequence coding for a soluble TNF inhibitory protein which has at its amino terminus the sequence Asp-Ser-Val-Cys-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-X-Asn-Ser, expression vectors, and prokaryotic and eukaryotic host cells, and recombinant production of the protein and recovering the protein. This is the same amino terminal sequence of SEQ ID NO: 4 of the instant invention. Wallach et al. purified this protein from human urine. Wallach also teaches that the host cells may be yeast, E.

coli and CHO cells (column 15, lines 11-35), and that the protein is formulated to comprise the polypeptide with a pharmaceutically acceptable carrier (column 16, lines 12-28). Therefore, Wallach et al. anticipates the claims. Later U.S. Patent 5,811,261 to Wallach et al. shows that the protein of SEQ ID NO: 2 is identical to the protein of SEQ ID NO: 2 of the instant invention, and the encoding portion of SEQ ID NO: 1 of Wallach et al. is identical to the encoding portion of SEQ ID NO: 1 of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 147 and 164 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallach et al., U.S. Patent No. 5,695,953, and further in view of Shadle et al., U.S. Patent No. 4,847,325, filing date Jan. 20, 1988.

Claims 147 and 164 encompass a method of recombinantly producing the pooyptpeide of SEQ ID NO: 4, recovering the polypeptide from the culture and chemically derivatizing the polypeptide.

The teachings of Wallach et al. are described above. Wallach et al. do not teach chemically derivatizing the protein. Wallach et al. teaches that there is evidence that over production of TNF-.alpha. can play a major pathogenic role in several diseases. Thus effects of TNF-alpha, primarily on the vasculature, are now known to be a major cause for symptoms of septic shock, and in some diseases, TNF may cause excessive loss of weight (cachexia) by suppresssing activities of adipocytes and by causing anorexia. It was also described as a mediator of the damage to tissues in rheumatic diseases and as a major mediator of the damage observed in graft-versus-host reactions, and there is therefore a necessity in finding out ways to eliminate or antagonize endogenously formed or exogenously administered TNF.

Shadle et al. teach that proteins can conjugated to a water-soluble polymer selected from polyethylene glycol or polypropylene glycol homopolymers, polyoxyethylated polyols, or polyvinyl alcohol, which results in a biologically active protein and has increased circulating half-life in mammals, compared to that of the unconjugated protein.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to chemically derivatize the TNF binding protein of Wallach et al. with a compound such as PEG, since Shadle et al. teaches that the half-life of the protein would be increased *in vivo*. One of ordinary skill in the art would be motivated to make a TNF binding protein that is more stable in vivo, since Wallach et al. teaches that many diseases are caused by the overproduction of TNF, and that the TNF binding protein can be used as an antagonist to

TNF *in vivo*. There would be a reasonable expectation of success, since this method of derivatization has been successfully used on a number of different protein.

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

EILEEN B. O'HARA
PATENT EXAMINER